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Request for grant of a patent

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1. Your reference PCS22001FAE-PROV2

2. Patent application number *(The Patent Office will fill in this part)* 0110251.6 26 APR 2001

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

PFIZER LIMITED
RAMSGATE ROAD
SANDWICH
KENT CT13 9NJ

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation UNITED KINGDOM

4. Title of the invention PROCESS FOR THE PREPARATION OF PYRAZOLO[4,3-d]PYRIMIDIN-7-ONE COMPOUNDS AND INTERMEDIATES THEREOF

5. Name of your agent *(if you have one)* DR. F.A. EDWARDS

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

PFIZER LIMITED
RAMSGATE ROAD
SANDWICH
KENT CT13 9NJ

127100

Patents ADP number *(if you know it)*

	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number			

	Number of earlier application	Date of filing *(day / month / year)*
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	42
Claim(s)	6
Abstract	1
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10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 26th April 2001

12. Name and daytime telephone number of person to contact in the United Kingdom: Dr. F.A. Edwards 01304.641687

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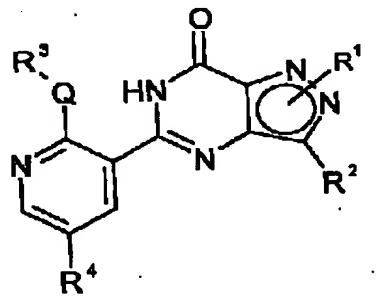
PCS22001FAE_PROV2

Process For The Preparation of Pyrazolo[4,3-d]pyrimidin-7-one Compounds and Intermediates Thereof

This invention relates to a series of pyrazolo[4,3-d]pyrimidin-7-one compounds of formula I (as defined below) and intermediates thereof. More notably, most of the compounds of interest are inhibitors of type 5 cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE5) and have utility in a variety of therapeutic areas (such as male erectile dysfunction). A compound of particular interest is 5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (hereinafter compound of formula IA).

Processes for the preparation of compounds of formula I are disclosed in WO 01/27112. In particular, example 132 of WO 01/27112 discloses a cyclisation reaction for preparing compound IA.

According to a first aspect of the invention there is provided a process for the preparation of a compound of formula (I):



I

or a pharmaceutically or veterinarily acceptable salt , pro-drug, polymorph and/or solvate thereof, wherein

Q represents O or NR^5

R^1 represents H, lower alkyl, Het, alkylHet, aryl or alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more substituents

selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

R^2 represents H, halo, cyano, nitro, OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$, $SO_2NR^{14}R^{15}$, lower alkyl, Het, alkylHet, aryl or alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

R^3 represents H, lower alkyl, alkylHet or alkylaryl (which latter three groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

R^4 represents H, halo, cyano, nitro, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$, $NR^{16}Y(O)R^{17}$, $N[Y(O)R^{17}]_2$, SOR^{18}, SO_2R^{19}, C(O)AZ, lower alkyl, lower alkenyl, lower alkynyl, Het, alkylHet, aryl, alkylaryl (which latter seven groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

Y represents C or S(O)

A represents lower alkylene

Z represents OR^6, halo, Het or aryl (which latter two groups are both optionally substituted with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

R^{10} and R^{11} independently represent H or lower alkyl (which latter group is optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10a}R^{11a}$, $NR^{12}R^{13}$, $SO_2NR^{14}R^{15}$ and $NR^{20}S(O)_2R^{21}$ or Het or aryl optionally substituted with one or more of said latter thirteen groups) or one of R^{10} and R^{11} may be lower alkoxy, amino or Het, which latter two groups are both optionally substituted with lower alkyl

R^{10a} and R^{11a} independently represent R^{10} and R^{11} as defined above, except that they do not represent groups that include lower alkyl, Het or aryl, when these three groups are substituted and/or terminated (as appropriate) by one or more substituents that include one or more $C(O)NR^{10a}R^{11a}$ and/or $NR^{12}R^{13}$ groups

R^{12} and R^{13} independently represent H or lower alkyl (which latter group is optionally substituted and/or terminated with one or more substituents selected from OR^6, $C(O)OR^9$, $C(O)NR^{22}R^{23}$ and $NR^{24}R^{25}$), one of R^{12} or R^{13} may be C(O)-lower alkyl or C(O)Het (in which Het is optionally substituted with lower alkyl), or R^{12} and R^{13} together represent C_{3-7} alkylene (which alkylene group is optionally unsaturated, optionally substituted by one or more lower alkyl groups and/or optionally interrupted by O or NR^{26})

R^{14} and R^{15} independently represent H or lower alkyl or R^{14} and R^{15}, together with the nitrogen atom to which they are bound, form a heterocyclic ring

R^{16} and R^{17} independently represent H or lower alkyl (which latter group is optionally substituted and/or terminated with one or more substituents selected from OR^6, $C(O)OR^9$, $C(O)NR^{22}R^{23}$ and $NR^{24}R^{25}$) or one of R^{16} and R^{17} may be Het or aryl, which latter two groups are both optionally substituted with lower alkyl

R^5, R^6, R^7, R^8, R^9, R^{18}, R^{19}, R^{20}, R^{22}, R^{23}, R^{24} and R^{25} independently represent H or lower alkyl

R^{18} and R^{19} independently represent lower alkyl

R^{21} represents lower alkyl or aryl

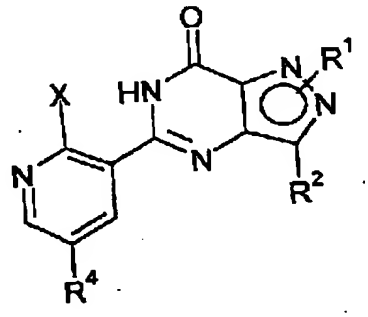
R^{26} represents H, lower alkyl, aryl, $C(O)R^{27}$ or $S(O)_2R^{28}$

R^{27} represents H, lower alkyl or aryl

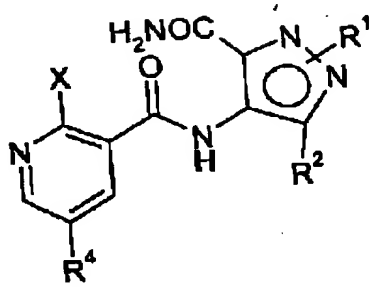
R^{28} represents lower alkyl or aryl

Het represents an optionally substituted four- to twelve-membered heterocyclic group, which group contains one or more heteroatoms selected from nitrogen, oxygen, sulphur and mixtures thereof

said process comprising reacting a compound of formula (II), (III), (IV) or (V) in the presence of $^-OR^3$ and a hydroxide trapping agent or, alternatively, in the case of compounds of formulae (IV) or (V) reacting in the presence of an auxiliary base and a hydroxide trapping agent. An auxiliary base as defined herein means a base other than $^-OR^3$ which is used in place of $^-OR^3$.



(II)



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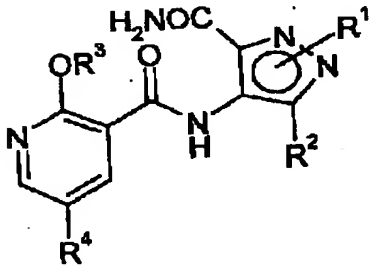
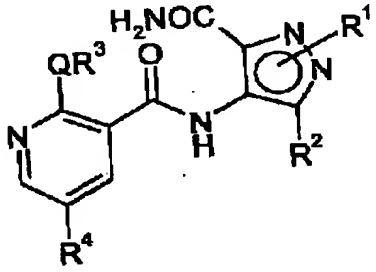


(IV)



(V)

wherein X is a leaving group and Q and R^1 to R^4 are as defined above.

The term "aryl", when used herein, includes six- to ten-membered carbocyclic aromatic groups, such as phenyl and naphthyl, which groups are optionally substituted with one or more substituents selected from aryl (which group may not be substituted by any further aryl groups), lower alkyl, Het, halo, cyano, nitro, OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10a}R^{11a}$, $NR^{12a}R^{13a}$ (wherein R^{12a} and R^{13a} independently represent R^{12} and R^{13} as hereinbefore defined, except that: (i) they do not represent C(O)Het in which Het is substituted by one or more substituents that include one or more $C(O)NR^{10a}R^{11a}$ and/or $NR^{12a}R^{13a}$ groups; or (ii) they do not together represent C_{3-7} alkylene interrupted by NR^{26}) and $SO_2NR^{14}R^{15}$.

The term "Het", when used herein, includes four- to twelve-membered, preferably four- to ten-membered, ring systems, which rings contain one or more heteroatoms selected from nitrogen, oxygen, sulfur and mixtures thereof, and which rings may contain one or more double bonds or be non-aromatic, partly aromatic or wholly aromatic in character. The ring systems may be monocyclic, bicyclic or fused. Each "Het" group identified herein is optionally substituted by one or more substituents selected from halo, cyano, nitro, oxo, lower alkyl (which alkyl group may itself be optionally substituted or terminated as defined below), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10a}R^{11a}$, $NR^{12a}R^{13a}$ and $SO_2NR^{14}R^{15}$. The term thus includes groups such as optionally substituted azetidinyl, pyrrolidinyl, imidazolyl, indolyl, furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxatriazolyl, thiatriazolyl, pyridazinyl, morpholinyl, pyrimidinyl, pyrazinyl, pyridinyl, quinolinyl, isoquinolinyl, piperidinyl, pyrazolyl imidazopyridinyl and piperazinyl. Substitution at Het may be at a carbon atom of the Het ring or, where appropriate, at one or more of the heteroatoms.

"Het" groups may also be in the form of an *N*-oxide.

The heterocyclic ring that R^{14} and R^{15} (together with the nitrogen atom to which they are bound) may represent may be any heterocyclic ring that contains at least one nitrogen atom, and which ring forms a stable structure when attached to the remainder of the molecule *via* the essential nitrogen atom (which, for the avoidance of doubt, is the atom to which R^{14} and R^{15} are attached). In this respect, heterocyclic rings that R^{14} and R^{15} (together with the nitrogen atom to which they are bound) may represent include four- to twelve-membered, preferably four- to ten-membered, ring systems, which rings contain at least one nitrogen atom and optionally contain one or more further heteroatoms selected from nitrogen, oxygen and/or sulfur, and which rings may contain one or more double bonds or be non-aromatic, partly aromatic or wholly aromatic in character. The term thus includes groups such as azetidinyl, pyrrolidinyl, imidazolyl, indolyl, isoazoyl, oxazoyl, triazolyl, tetrazolyl, morpholinyl, piperidinyl, pyrazolyl and piperazinyl.

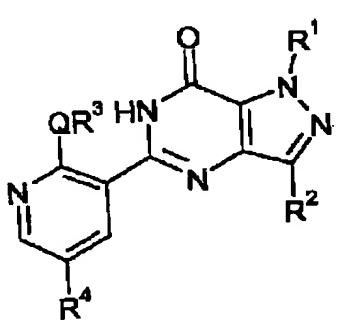
The term "lower alkyl" (which includes the alkyl part of alkylHet and alkylaryl groups), when used herein, means C_{1-6} alkyl and includes methyl, ethyl, propyl, butyl, pentyl and hexyl groups. Unless otherwise specified, alkyl groups may, when there is a sufficient number of carbon atoms, be linear or branched, be saturated or unsaturated, be cyclic, acyclic or part cyclic/acyclic, and/or be substituted by one or more halo atoms. Preferred lower alkyl groups for use herein are C_{1-3} alkyl groups. Alkyl groups which R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27} and R^{28} may represent, and with which R^1, R^2, R^3, R^4, R^{10}, R^{11}, R^{12}, R^{13}, R^{16}, R^{17}, aryl, alkylaryl, alkylHet and Het may be substituted, may, when there is a sufficient number of carbon atoms, be linear or branched, be saturated or unsaturated, be cyclic, acyclic or part cyclic/acyclic, be interrupted by one or more of oxygen, sulfur and optionally alkylated or optionally acylated nitrogen and/or be substituted by one or more halo atom. The terms "lower alkenyl" and "lower alkynyl", when used herein, include C_{2-6} groups having one or more double or triple carbon-carbon bonds, respectively. Otherwise, the terms "lower alkenyl" and "lower alkynyl" are defined in the same way as the term "lower alkyl". Similarly, the term "lower alkylene", when used herein, includes C_{1-6} groups which can be bonded at two places on the group and is otherwise defined in the same way as "lower alkyl". The term "acyl" includes C(O)-lower alkyl.

In the above definition, unless otherwise indicated, alkyl, alkoxy and alkenyl groups having three or more carbon atoms, and alkanoyl groups having four or more carbon atoms, may be straight chain or branched chain.

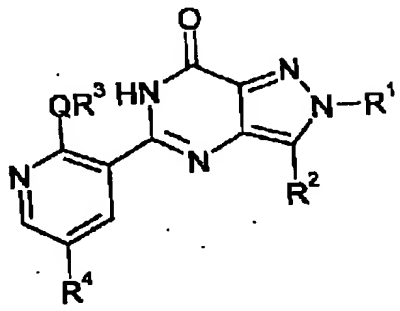
The terms "alkylHet" and "alkylaryl" include C_{1-6} alkylHet and C_{1-6} alkylaryl. The alkyl groups (e.g. the C_{1-6} alkyl groups) of alkylHet and alkylaryl may, when there is a sufficient number of carbon atoms, be linear or branched, be saturated or unsaturated, and/or be interrupted by oxygen. When used in this context, the terms "Het" and "aryl" are as defined hereinbefore. Substituted alkylHet and alkylaryl may have substituents on the ring and/or on the alkyl chain.

Halo groups with which the above-mentioned groups may be substituted or terminated include fluoro, chloro, bromo and iodo and the terms haloalkyl and haloalkoxy include CF_3 and OCF_3 respectively.

Compounds of general formula (I) can be represented by formulae I' and I'':



(I')

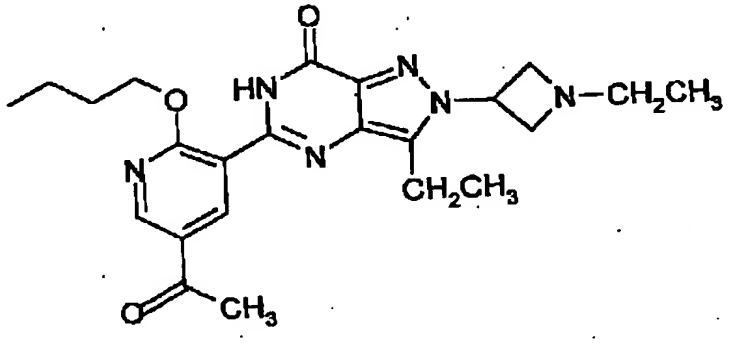


(I'')

wherein R^1, R^2, R^3, R^4 and Q are as defined hereinbefore.

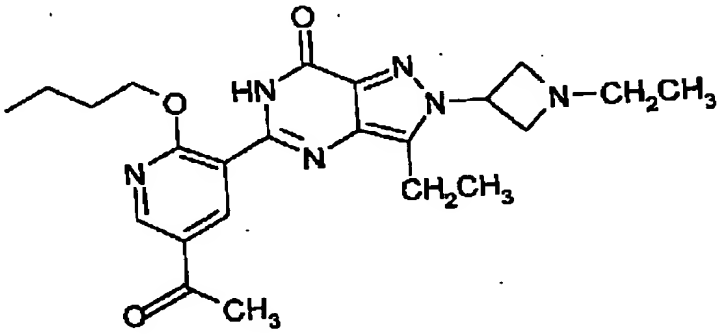
The compounds of formulae (I) may contain one or more chiral centres and therefore can exist as stereoisomers, i.e. as enantiomers or diastereoisomers, as well as mixtures thereof. The invention relates to formation of both the individual stereoisomers of the compounds of formulae (I) and any mixture thereof.

In a first preferred embodiment of the invention a compound of formulae (IA) is prepared.



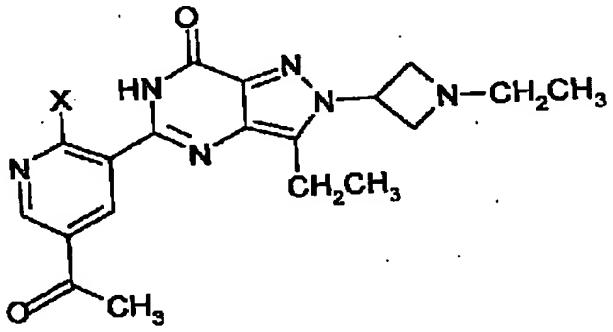
(IA)

Accordingly, in a preferred aspect of the invention there is provided a process for the preparation of a compound of formula (IA).

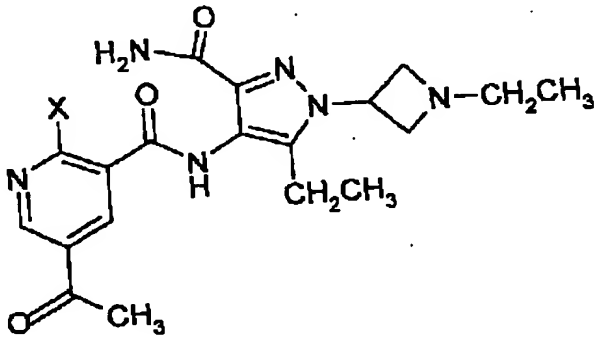


(IA)

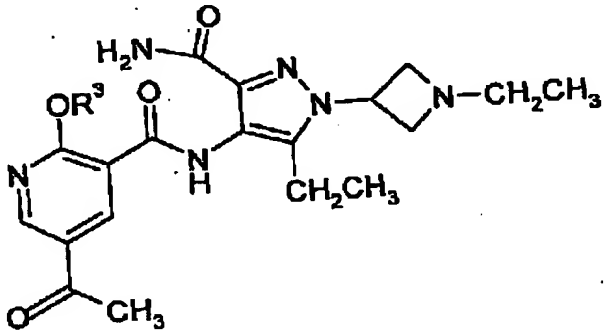
comprising reacting a compound of formula (IIA), (IIIA) or (IVA) respectively



(IIA)



(IIIA)



(IVA)

In the presence of $^{-}OR^{3}$ and a hydroxide trapping agent, or alternatively in the case of compounds of formula (IVA) reacting in the presence of a hydroxide trapping agent and an auxiliary base, wherein OR^{3} in the case of formation of compound (IA) and (IVA) is $CH_3(CH_2)_3O$- and wherein X in formulae (IIA) and (IIIA) is a leaving group.

Intermediates of the general formula (IIA), (IIIA) and (IVA), where novel, form further aspects of the invention.

As a result of use of the hydroxide trapping agent, a particular advantage of the present process is that a high yield of final product (compounds of formula (I, IA) and intermediate compounds (II, IIA) can be obtained.

In a preferred embodiment compounds of formula (I) can be obtained in good yield without intermediate isolation.

It is most advantageous to form the compounds of formula (I) from intermediates of formula (III) since the cyclisation step (III to II) and the nucleophilic displacement of X by $^-OR^3$ (II to I) can be carried out in a one-pot reaction. Furthermore this process can be run at ambient pressure whereas the cyclisation step of the 2 step process can require higher pressures where XH is a lower alkanol, such as methanol, ethanol or isomers of propanol.

In a further aspect of the invention, there is provided a process for the formation of compounds of formula (II) (more particularly IIA wherein X in II / IIA = $-OR^3$) comprising the cyclisation of compounds of formula (III) (more particularly IIIA) wherein X is a leaving group as defined hereinbefore, in the presence of said hydroxide trapping agent. Again, this step benefits from the higher yield provided by using the hydroxide trapping agent.

Of course, the trapping agent technology could be used to form compounds of formula (IV) (more particularly IVA) from compounds of formula (III) (more particularly IIIA) in the presence of $^-OR^3$, advantageously up to about 1 molar equivalent of $^-OR^3$ (to compounds (III)). If substantially more than 1 equivalent of $^-OR^3$ was used, the reaction would proceed through to compounds (I) (more particularly IA).

Preferably the hydroxide trapping agent is an ester.

More preferably said hydroxide trapping agent is an ester of the formula:

TOC(O)W

wherein OT is OR^3 as defined hereinbefore or, OT is the residue of a bulky alcohol or a non-nucleophilic alcohol, or TOH is an alcohol which can be azeotropically removed during the reaction;

and C(O)W is the residue of a carboxylic acid.

For example, where X is OEt in compound (IIA) and (IIIA) the ester trapping agent can be n-butyl acetate (i.e. OT=X and C(O)W is a residue of acetic acid), or ethyl acetate or ethyl pivalate, more preferably butyl pivalate (OT=X and C(O)W is the residue of pivalic acid- i.e. a carboxylic acid with no enolisable proton).

In a most preferred process, wherein X is OEt in compound (IIA) or (IIIA) the ester trapping agent is butyl actetate.

Preferably X is selected from the group consisting of optionally substituted arylsulphonyloxy, preferably phenylsulphonyloxy, more preferably a para substituted aryl (phenyl) such as by a C_1-C_4 alkyl group e.g. p-toluenesulphonyloxy; C_1-C_4 alkylsulphonyloxy e.g. methanesulphonyloxy; nitro or halo substituted benzenesulphonyloxy preferably para substituted e.g. p-bromobenzenesulfonyloxy or p-nitrobenzenesulphonyloxy; C_1-C_4 perfluoroalkylsulphonyloxy e.g. trifluoromethylsulphonyloxy; optionally substituted aroyloxy such as benzoyloxy; C_1-C_4 perfluoroalkanoyloxy such as trifluoroacetyloxy; C_1-C_4 alkanoyloxy such as acetyloxy; halo; diazonium; C_1-C_6 primary and secondary alkoxy such as methoxy; quatenaryammonium C_1-C_4 alkylsulphonyloxy; halosulphonyloxy e.g. fluorosulphonyloxy and other fluorinated leaving groups; and diarylsulphonylamino e.g. ditosyl (NTs_2).

Most preferably, for formation of compounds of formula (I) more particularly (IA), X is a C_1-C_4 alkoxy (advantageously ethoxy or methoxy) or halogen since this lends itself to simpler and cheaper formation of compounds - for example see Schemes 1 and 3 hereinafter.

An advantage of using labile leaving groups such as chloro or fluoro may be that an inert solvent could then be used rather than R^3OH (which will often be more expensive). Thus only a sufficient amount of $^-OR^3$ (such as from R^3OH) as reactant would be required.

$^-OR^3$ can act both as a nucleophile (to displace the leaving group by nucleophilic substitution) and as a base (to bring about the cyclisation).

$^-OR^3$ can be generated in solution from, for example, a salt ZOR^3 (wherein Z is a cation) such as a metal salt. More particularly an alkali (such as sodium or potassium) or alkaline earth metal salt of $^-OR^3$ in a suitable solvent would give rise to $^-OR^3$ in solution. For example, potassium butoxide, potassium amylate, KHMDS or NaHMDS in a suitable solvent, under suitable temperature conditions, such as 1-butanol, with intermediate (IIA) or (IIIA) would form compound (IA). In another embodiment, $^-OR^3$ can be formed *in situ* from R^3OH plus an auxiliary base (i.e. a base other than $^-OR^3$). However, in another system, ZOR^3 could be used in the reaction system with an auxillary base.

As will be appreciated the solvent in which the reaction takes place can be R^3OH or an inert solvent (or a mixture of both). By inert solvent we mean a solvent which will not form a nucleophile under the reaction conditions, or, if a nucleophile is formed it is sufficiently hindered or un-reactive such that it does not substantially compete in the displacement reaction. When R^3OH is used as a source of $^-OR^3$, then a separate solvent is not essentially required but an (auxiliary) inert solvent (i.e. a solvent other than R^3OH) may be used as a co-solvent in the reaction.

Suitable solvents are as follows:
R^3OH, a secondary or tertiary C_4-C_{12} alkanol, a C_5-C_{12} cycloalkanol, a tertiary C_4-C_{12} cycloalkanol, a secondary or tertiary (C_3-C_7 cycloalkyl)C_2-C_6 alkanol, a C_3-C_9 alkanone, 1,2-dimethoxyethane, 1,2-diethoxyethane, diglyme, tetrahydrofuran, 1,4-dioxan, toluene, xylene, chlorobenzene, 1,2-dichlorobenzene, acetonitrile, dimethyl

sulphoxide, sulpholane, dimethylformamide, N-methylpyrrolidin-2-one, pyridine, and mixtures thereof.

More preferably, the solvent is R^3OH, a tertiary C_4-C_{12} alkanol, a tertiary C_4-C_{12} cycloalkanol, a tertiary (C_3-C_7 cycloalkyl)C_2-C_6 alkanol, a C_3-C_9 alkanone, 1,2-dimethoxyethane, 1,2-diethoxyethane, diglyme, tetrahydrofuran, 1,4-dioxan, toluene, xylene, chlorobenzene, 1,2-dichlorobenzene, acetonitrile, dimethyl sulphoxide, sulpholane, dimethylformamide, N-methylpyrrolidin-2-one, pyridine, and mixtures thereof.

Most preferably the solvent is R^3OH, which means that $^-OR^3$ is formed *in situ*, such as, in the presence of an auxiliary base. For compound (IA) the solvent is preferably $CH_3(CH_2)_3OH$ (1-butanol).

A wide range of auxiliary bases can be used in the process of the invention. Typically the bases would not substantially compete with $-OR^3$ in the nucleophilic substitution of X (i.e. they would be non nucleophilic) such as by being suitably sterically hindered.

Preferably the auxiliary base is selected from the group consisting of a sterically hindered metal alkoxide base, a metal amide, a metal hydride, metal oxide, metal carbonate and metal bicarbonate.

Examples of suitable alcohol and amine metal salts include metal salts of: a secondary or tertiary C_4-C_{12} alkanol; a C_3-C_{12} cycloalkanol and a secondary or teritary (C_3-C_8 cycloalkyl)C_1-C_6 alkanol; a N-(secondary or tertiary C_3-C_6 alkyl)-N-(primary, secondary or tertiary C_3-C_6 alkyl)amine; a N-(C_3-C_8 cycloalkyl)-N-(primary, secondary or tertiary C_3-C_6 alkyl)amine; a di(C_3-C_8 cycloalkyl)amine or hexamethyldisilazane; or 1,5-diazabicyclo[4,3,0]non-5-ene and 1,8-diazabicyclo[5,4,0]undec-7-ene.

Examples of suitable metal salts of a tertiary C_4-C_6 alcohol such as the alkali or alkaline earth metal salts (e.g. Na/K) of t-butanol or t-amyl alcohol, or the base are: potassium t-butoxide, potassium hexamethyldisilazone (KHMDS) or NaHMDS.

More preferably the auxiliary base is a sterically hindered base selected from: metal salts of sterically hindered alcohols or amines; or metal carbonates. Preferred herein are metal carbonates, and advantageously potassium carbonate for the delivery of higher yield, improved impurity profile.

Further examples of suitable carbonate bases for use herein include sodium carbonate, caesium carbonate, lithium carbonate, rubidium carbonate, strontium carbonate, barium carbonate, beryllium carbonate and magnesium carbonate. Preferred for use herein are non-toxic carbonate bases with reasonably rapid reaction rate, in the cyclisation reaction according to the present invention. Potassium carbonate is especially preferred as defined hereinbefore.

Preferably the metal of the salt of ZOR^3 and the auxiliary base are independently selected from alkali metals (lithium, sodium, potassium, rubidium, caesium) or alkaline earth metals (beryllium, magnesium, calcium, strontium, barium). More preferably the metal is sodium or potassium and potassium is especially preferred.

To maximise yields, it is further preferred that at least about 1 molecular equivalent of auxiliary base and $-OR^3$ are used in accordance with the invention. If $-OR^3$ also functions as a base (i.e. there is no auxiliary base present) then preferably at least about 2 equivalents of $^-OR^3$ are present. Suitably, at least about 1 equivalent of trapping agent (preferably at least about 2 equivalents) is present. Especially preferred for use herein is about 3 equivalents of auxiliary base (preferably potassium carbonate) and at least about 1, preferably at least about 2 and especially about 3 equivalents of trapping agent (preferably butyl acetate)..

The temperature of the cyclisation reaction of compounds (III) and (IV) to (I) (such as for the corresponding formation of compound (IA)) is preferably at least about 80°C, more preferably about 80 to about 130°C, more preferably still about 100 to about 130°C and most preferably about 112°C to about 122°C. These temperatures are also applicable for the conversion of compounds (II) to (I), although the temperature in this case could also probably be lower (e.g. about 60°C) since there is no cyclisation taking place.

The reaction temperature attainable to effect the conversion of compounds of formulae (II) and (III) to compounds of formula (I) depends on the solvent, the nature of $^{-}OR^3$ and X. When X is an alkoxy and R^3OH is the solvent, preferably XH (such as C_{1-6} alkoxy) is removed azeotropically (of course the reaction vessel must be configured to distil over the azeotrope mixture) with R^3OH by running the reaction at the azeotrope temperature of XH and R^3OH. In this way the yield and quality of the final product can be further improved. For example, (where X is an alkoxy) the conversion of compound (IIA), (IIIA) or (IVA) to (IA) is preferably carried out at the azeotrope temperature of the alcohol i.e. XH (preferably methanol or ethanol, most preferably ethanol) and 1-butanol.

Thus according to further preferred embodiments the invention provides :

A process for the synthesis of compound (IA) by reaction of compound (IIA) or (IIIA):

a) with 1-butanol and auxiliary base, preferably potassium butoxide, optionally in an inert solvent such as toluene and in the presence of said trapping agent TOC(O)W; or

b) with $ZO(CH_2)_3CH_3$ and an auxiliary base in n-butanol or an inert solvent or both, in the presence of said trapping agent; or

c) with $ZO(CH_2)_3CH_3$ and n-butanol or an inert solvent or both, in the presence of said trapping agent.

Preferably, the trapping agent is $BuOC(O)W$ or $CH_3OC(O)W$ wherein C(O)W is a residue of a carboxylic acid (preferably sterically hindered) such as $CH_3(CH_2)_3OC(O)CH_3$ or $CH_3(CH_2)_3OC(O)(CH_3)_3$.

To maximise yields, it is further preferred that at least about 1 molecular equivalent of auxiliary base and $-OR^3$ are used in accordance with the invention. If $-OR^3$ also functions as a base (i.e. there is no auxiliary base present) then preferably at least about 2 equivalents of $^{-}OR^3$ are present. Thus to maximise yields of compounds (IA), suitably at least about 1 equivalent of trapping agent (preferably at least about 2 equivalents) is present. With respect to (a) above, preferably there is at least about 2

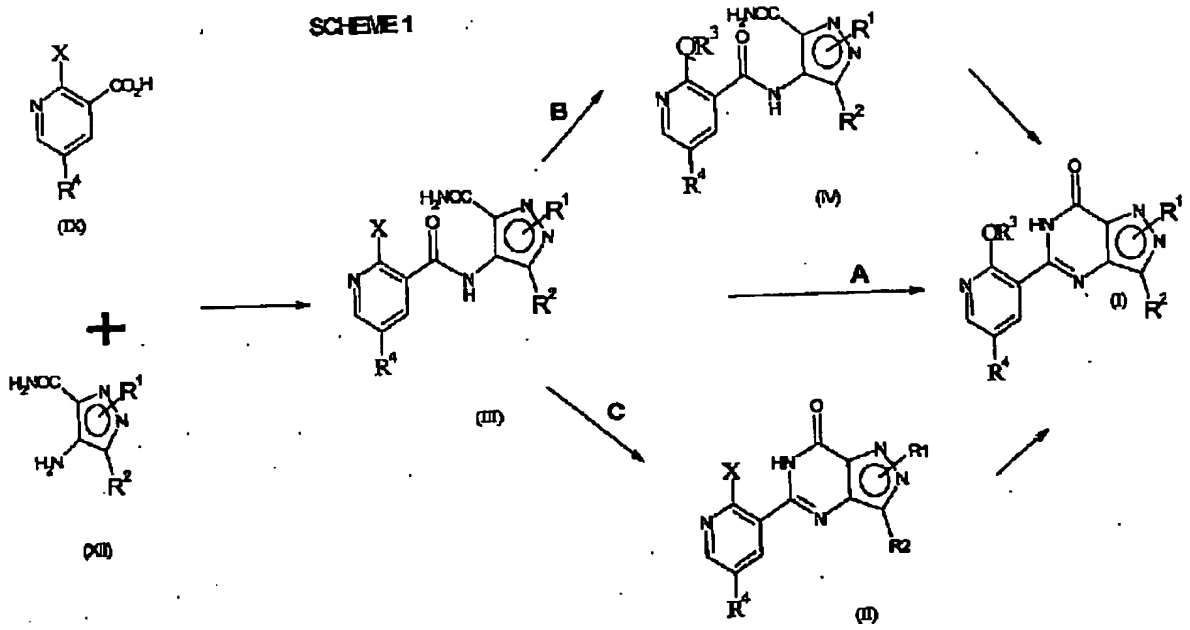
molecular equivalents of base and at least about 1 molecular equivalent of trapping agent relative to the substrate (more preferably at least about 2.2 and 2.5 respectively). For (b) above, preferably there is at least about 1 molecular equivalent of auxiliary base, trapping agent and $ZO(CH_2)_3CH_3$ relative to the substrate (more preferably at least about 1.2 equivalents of auxiliary base and at least about 2.5 equivalents of trapping agent). For (c) above, preferably there is at least about 2 molecular equivalents of $ZO(CH_2)_3CH_3$ and at least about 1 equivalent of trapping agent relative to the substrate (more preferably at least about 2 and 2.5 equivalents respectively).

To further improve yields of final product and reduce impurities, preferably C(O)W is the residue of a sterically hindered carboxylic acid and/or a carboxylic acid which does not contain an enolisable proton (e.g. pivalic acid).

The compounds of general formula (III) and (IIIA) may be obtained from readily available starting materials for example, by the routes depicted in the following reaction schemes. Reaction Scheme 1 illustrates for preparation of compounds of compounds of general formula (I) from compounds of formulae (IX) and (XII).

Compound (III) is formed by reaction of intermediate (IX) and compound (XII) in the presence of a coupling agent, such as N,N'-carbonyldiimidazole and a suitable solvent, such as ethyl acetate.

SCHEME 1



wherein R^1, R^2, R^3, R^4, X and Q are as defined hereinbefore.

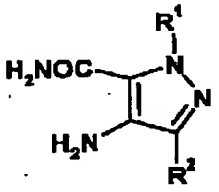
Further suitable conditions for the coupling of compounds of formulae (XII) and (IX) to provide compounds of formula (III) include: conventional amide bond-forming techniques, e.g. via the acyl chloride derivative of (IX) in the presence of up to about a five-fold excess of a tertiary amine such as triethylamine or pyridine to act as scavenger for the acid by-product (e.g. HCl), optionally in the presence of a catalyst such as 4-dimethylaminopyridine, in a suitable solvent such as dichloromethane, at from about 0°C to about room temperature. For convenience pyridine may also be used as the solvent.

In particular, any one of a host of amino acid coupling variations may be used. For example, the acid of formula (IX) or a suitable salt (e.g. sodium salt) thereof may be activated using a carbodiimide such as 1,3-dicyclohexylcarbodiimide or 1-ethyl-3-(3-dimethylaminoprop-1-yl)carbodiimide optionally in the presence of 1-hydroxybenzotriazole hydrate and/or a catalyst such as 4-dimethylaminopyridine, or

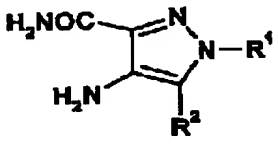
by using a halotrisaminophosphonium salt such as for example bromotris(pyrrolidino)phosphonium hexafluorophosphate or by using a suitable pyridinium salt such as 2-chloro-1-methylpyridinium iodide. Either type of coupling is conducted in a suitable solvent such as dichloromethane, tetrahydrofuran or N,N-dimethylformamide, optionally in the presence of a tertiary amine such as triethylamine or N-ethyldiisopropylamine (for example when either the compound of formula (XII), or the activating reagent – for the acid of formula (IX), is presented in the form of an acid addition salt), at from about 0°C to about room temperature. Preferably, from 1 to 2 molecular equivalents of the activating reagent and from 1 to 3 molecular equivalents of any tertiary amine present are employed.

In a further variation, the carboxylic acid function of acid (IX) may first of all be activated using up to about a 5% excess of a reagent such as N,N-carbonyldiimidazole in a suitable solvent, e.g. ethyl acetate or butan-2-one, at from about room temperature to about 80°C, followed by reaction of the intermediate imidazolide with (XII) at from about 20°C to about 90°C.

It will be appreciated that the general formula (XII) can also be represented by the regioisomeric formulae (XII') and (XII''):



(XII')



(XII'')

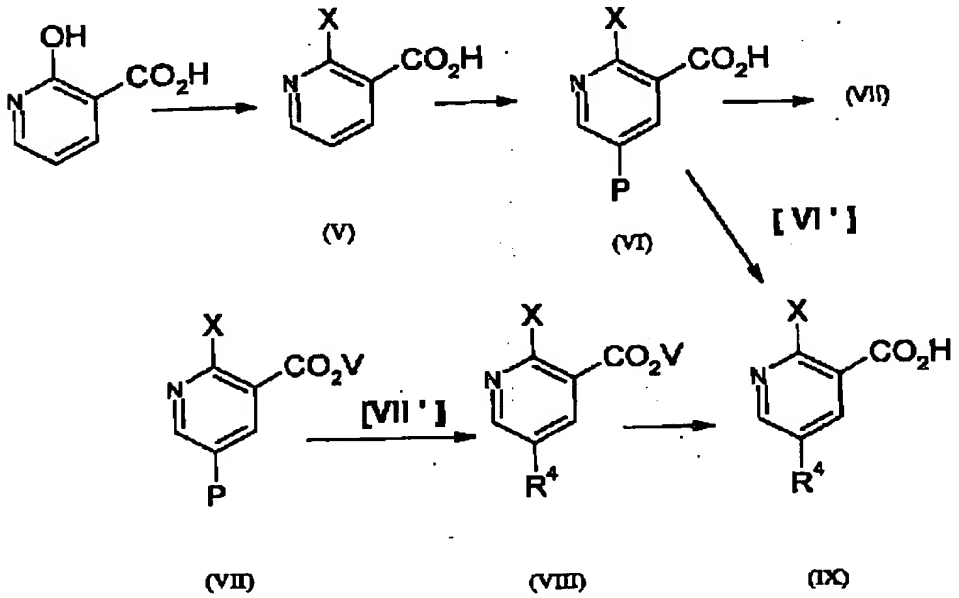
wherein R^1 and R^2 are as previously defined herein.

In Scheme 1 the compounds of general formula (I) can be prepared from compounds of general formula (III) by: cyclisation directly to a compound of formula (I), route A; exchange of "X" for "QR^3 followed by cyclisation of compound (IV) to a compound of formula (I), route B; or by cyclisation to form a compound (II) followed by exchange of "X" for "OR^3", route C. The cyclisation of route A includes both cyclisation where X =

OR^3 as well as cyclisation with alkoxide exchange where X is exchanged for OR^3. Routes A, B and C are in a preferred process according to the present invention carried out in a one-pot process without isolation of intermediate compounds, such as for example compounds (II) or (IV).

Reaction Scheme 2 illustrates the preparation of compounds of general formula (IX) starting from the commercially available material, 2-hydroxynicotinic acid.

SCHEME 2



In the compounds of Scheme 2, X and R^4 are as hereinbefore defined. P is a group which can undergo an oxidative addition reaction with Palladium (0), such as for example halogen, trifluoromethanesulfonate, perfluoroethane sulfonate, diazonium salts and is preferably F, Cl, Br or I, more preferably Br or I. V is any suitable carboxylic acid protecting group such as: C_1-C_4 alkyl esters, preferably ethyl or methyl esters; aryl groups such as benzyl; or a silicon protecting group such as a trimethylsilyl (TMS) group.

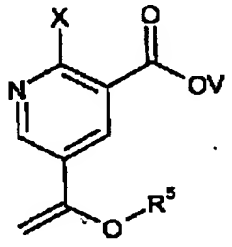
As illustrated in Scheme 2, where not commercially available, the intermediate of formula (V) can be formed from commercially available starting materials such as 2-chloronicotinic acid or 2-hydroxynicotinic acid or a salt thereof by routine synthetic methods such as are exemplified hereinafter in the preparations section.

Intermediate compounds of formula (IX) wherein X = OR^{3a} wherein OR^{3a} is a different alkoxy group from OR^3 wherein R^{3a} is a C_1-C_6 alkyl group, preferably a C_1-C_4 alkyl group and R^4 is as defined hereinbefore can be formed from compounds of formula (VIII) (wherein X = OR^{3a} and R^4 are as defined for (IX) and V is as defined hereinbefore) by hydrolysis, when V is an alkyl or aryl group, (IX) is preferably formed via base hydrolysis with metal hydroxide, more preferably with sodium hydroxide. Where V is a benzyl or silyl group, (IX) is formed via hydrogenation.

Compounds of formula (VIII) wherein X = OR^{3a} and R^4 and V are as defined herein before, can be formed from compounds of formula (VII) (wherein X = OR^{3a} and V are as defined for (VII) and P is as defined hereinbefore) via a substitution reaction (wherein group P is exchanged for the desired R^4 moiety), and preferably wherein such substitution reaction is a metal-mediated reaction. According to a preferred process said conversion is affected via acylation under Heck conditions as exemplified hereinafter.

Accordingly the present invention provides a process for the conversion of compound (VII) (wherein P = Br or I, wherein X = OEt and wherein V is as defined hereinbefore) to compound (VIII) (wherein R^4 = $C(O)CH_3$ and X = OEt and V is as defined hereinbefore) such as via reaction with butylvinyl ether and triethylamine in a suitable solvent, such as for example acetonitrile, dimethyl formamide (DMF), dimethyl acetamide (DMAC), N-methyl pyrrolidone (NMP) or water, under reflux conditions and at atmospheric pressure wherein said reaction is carried out in the presence of a suitable catalyst such as palladium acetate and a ligand such as tri-o-tolyl phosphine wherein the ratio of compound (VII) to acylating agent is about 1 : 15, preferably about 1 : 8, more preferably about 1 : 10 molecular equivalents and wherein the ratio

of compound (VII) to base is about 1 : 2.0, preferably about 1 : 1.5 molecular equivalents and wherein the ratio of compound (VII) to catalyst in about 1 : 0.25, preferably about 1 : 0.16 molecular equivalents. To ensure appropriate conversion of the non-isolated intermediate enol-ether compound VIII' to the desired ester VIII the reaction should have an aqueous acidic work-up.



VIII'

wherein X and V are as defined hereinbefore and wherein R^5 is a C_1-C_5 alkyl group, preferably C_1-C_4 alkyl and especially butyl.

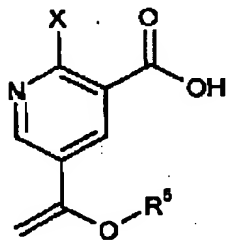
Compounds of formula (VII) wherein X = OR^{3a} and V and P are as defined hereinbefore, and preferably wherein X = (C_1-C_4) primary or secondary alkoxy and P is a halogen, can be formed from compounds of formula (VI) (wherein X and P are as defined for (VII)) in an esterification/protection reaction via treatment with a suitable acid catalyst and an alcohol of formula V-OH, or treatment with a suitable base and an alkylating agent wherein V is as defined hereinbefore, and wherein V is preferably C_1-C_4 alkyl. Preferred conditions wherein X = OEt; V-OH = CH_3-OH include: treatment with an HCl/H_2SO_4 mixture; or treatment with H_2SO_4; or treatment with ethyl iodide and cesium cabonate.

Compounds of formula (VI) (wherein X = OR^{3a} and P is as previously defined) can be formed from compounds of formula (V) wherein X= OR^{3a} via a halogenation reaction

such as bromination with a suitable electrophilic halogenation agent i.e. N-bromosuccinamide.

It is possible to undertake the three step conversion of (VI) to (IX) (more particularly (VIA) to (IXA), see Scheme 5 hereinafter) in a single step.

Thus according to a highly preferred process of the invention and as illustrated in Scheme 2, compounds of general formula (VI) can be transformed directly into compounds of general formula (IX). Such direct transformation reactions proceed via a non isolated intermediate compound of general formula VI' as illustrated below:



VI'

wherein X is as defined herein before.

In such a highly preferred process compounds of formula (IX) can be prepared directly from compounds of formula (VI) in a one-step reaction. Suitable reagents for such direct conversion of compounds of formula (VI) to compounds of formula (IX) wherein X = OR^{3a}, preferably wherein X = OEt, and wherein P = a halogen, preferably Br, include using butyl vinyl ether and triethylamine in acetonitrile solvent at reflux temperature and at ambient/atmospheric pressure in the presence of catalyst such as palladium acetate and ligand such as tri-o-tolyl phosphine. For such reactions suitable reagent amount are (i) the ratio of base to compound (VI) is more

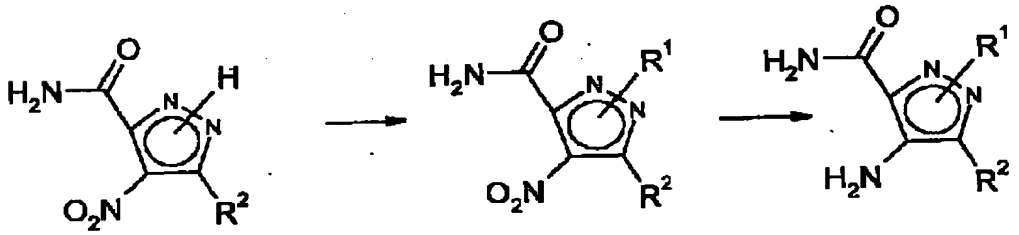
than about 1.5 : 1, preferably more than about 2.0 : 1 and more preferably about 2.5 : 1 molecular equivalents and/or ; (ii) the ratio of acylating agent to compound (VI) is about 2.5 : 1 to about 5 : 1, preferably about 2.5: 1 to about 3.5 : 1 and especially about 3 : 1 molecular equivalents. Especially preferred herein for the provision of high yield of (XI) are such reactions wherein in addition to the aforementioned preferred ratios of acid (VI) to base and/or acylating agent, the ratio of acid (VI) to catalyst is about 1 : 0.04 molecular equivalents.

It is especially surprising that the above highly preferred conditions furnished higher yields of (IX) versus similar reactions where a higher catalyst level was utilised.

Following the initial reaction of compound (VI) with the base, acylating agent and catalyst in an appropriate solvent it is necessary that the reaction mixture is subjected to an aqueous acidic work-up in order to furnish the desired compound of formula (IX) rather than the intermediate enol-ether (VI') as detailed hereinbefore.

Reaction Scheme 3 illustrates the preparation of compounds of general formula (XI).

SCHEME 3



(X) (XI) (XII)

wherein R^1 and R^2 are as defined hereinbefore.

With reference to Scheme 3 compounds of formula (XII) can be formed from compounds of formula (XI) via a suitable reduction reaction such as with palladium on charcoal and hydrogen, under pressure where necessary. Compounds of formula (XI) can be formed from compounds of formula (X) via a suitable alkylation, arylation or acylation reaction.

Reaction Schemes 4 to 6 provide the corresponding intermediate compounds and transformations for the preparation of highly preferred compound (IA).

Scheme 4 illustrates a preferred process for the coupling of preferred compounds (IXA) and (XIIA) to provide compound of formula (IIIA) which are then cyclised to provide the compound of formula (IA) according to the process of the present invention.

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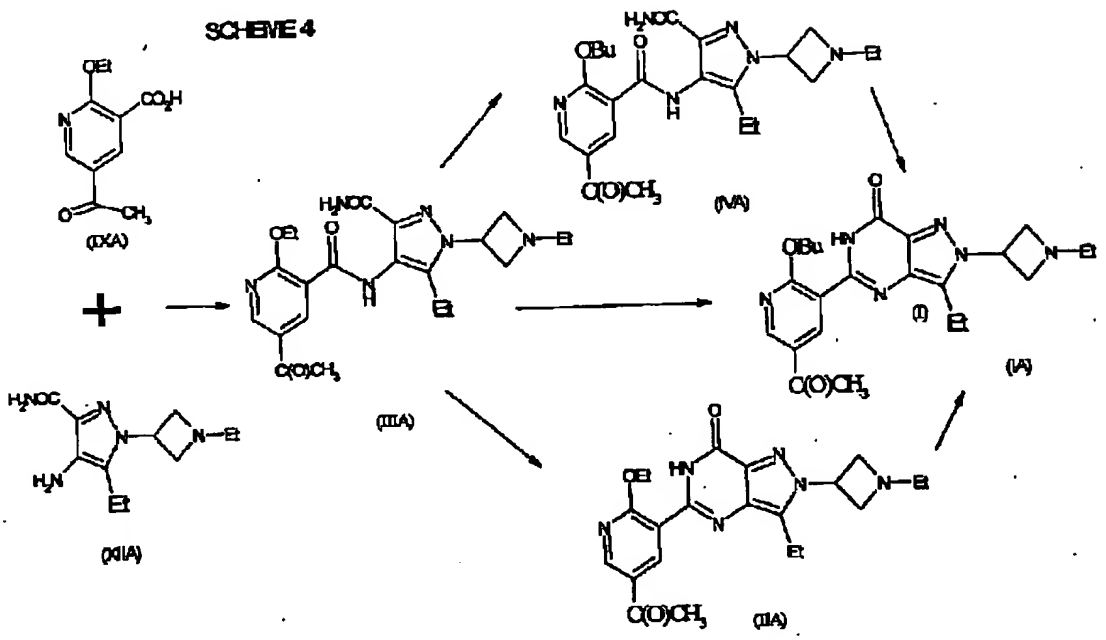
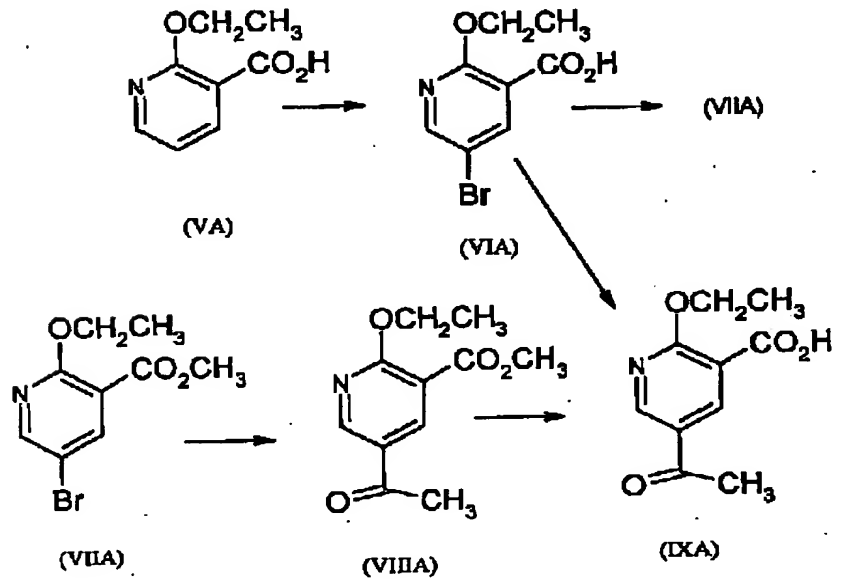
SCHEME 4



Reaction Scheme 5 illustrates a preferred process for the preparation of compounds of formula (IXA).

SCHEME 5



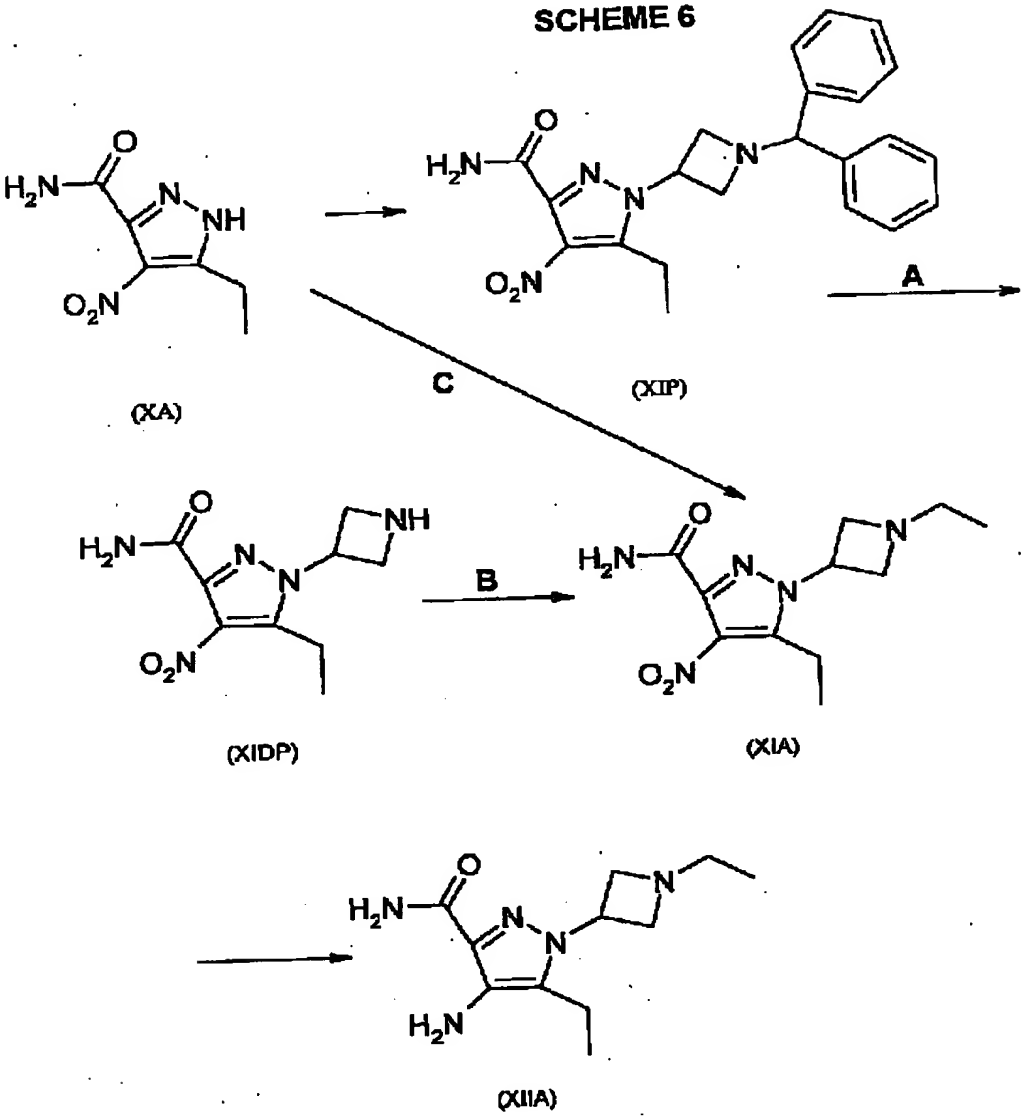
Scheme 5 illustrates a preferred embodiment for the formation of compound (IX) as generally described in Scheme 2, wherein X is an alkoxy (and so X in compound VA represents OR^{3a}), more preferably a C_{1-6} primary or secondary alkoxy, such as ethoxy.

Compounds of the general formula (IXA) are prepared according to methods shown in Examples section hereinafter.

According to a highly preferred process herein compound (IXA) is prepared directly from compound (VIA) by reaction with acylating agent, base and catalyst wherein the ratio of compound (VIA): acylating agent : base : catalyst is about 1 : 3 : 2.5 : 0.04 molecular equivalents. In an especially preferred process the acylating agent is butyl vinyl ether, the base is triethylamine, the catalyst is $Pd(OAc)_2$, the solvent is acetonitrile and the ligand is tri-o-tolyl phosphine and the reaction is carried out under reflux conditions at atmospheric pressure. Such preferred process is illustrated at preparation 1 hereinafter.

Reaction Scheme 6 illustrates the preparation of compounds of general formula (XIIA) as generally detailed in Scheme 3.

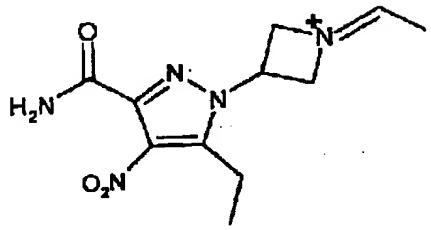
SCHEME 6



(XA) (XIP) (XIDP) (XIA) (XIIA)

Compounds of formula (XIIA) can be formed from compounds of formula (XIA) via hydrogenation such as via treatment with palladium/charcoal and hydrogen and as exemplified herein at preparation 9 hereinafter.

Compounds of formula (XIA) can be formed from compounds of formula (XIDP) via a two stage process of: (i) amination (to prepare an intermediate Imine of general formula (XIDP') as illustrated below:



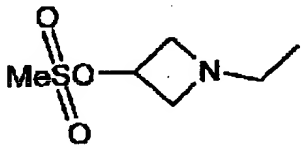
XIDP'

such as via treatment with acetaldehyde or a synthetic equivalent followed by; (ii) reduction such as with $Na(OAc)_3BH$ to furnish the desired compound of formula (XIA) and as exemplified herein at preparation 8 hereinafter.

Compounds of formula (XIDP) can be formed from compounds of formula (XIP) via de-protection of the N-protecting benzhydryl group using suitable de-protection conditions such as exemplified at preparation 7 hereinafter.

Compounds of formula (XIP) can be formed from compounds of formula (XA) according to the processes at preparations 6(a) and 6(b) hereinafter. The process of preparation 6(b) is particularly preferred herein as it provides higher yields.

According to a further aspect of the process hereinbefore described for the preparation of compounds of the general formula (XIA), such compounds can be prepared from compounds (XA) via a "one-step" process via reaction with the compound:



wherein such reaction takes place in a suitable non nucleophilic solvent, such as for example THF.

According to a particularly preferred process herein compounds of the general formula (XIA) can be prepared directly from compounds of the formula (XA). An advantage of such direct transformation is process efficiency.

Compound (IIIA) is formed by reaction of intermediate (IX) and 4-Amino-5-ethyl-1 (2-ethyl-azetidinyl)-1H-pyrazole-3-carboxamide (compound XII) in the presence of a coupling agent, such as 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride and where desirable also in the presence of a base and/or an accelerator. In one example of a coupling system, the carboxylic acid function of (VIA) is first of all activated using molar equivalent of a reagent such as N,N-carbonyldimidazole (as coupling agent) in a suitable solvent, e.g. ethyl acetate, at from about room temperature to about 80°C, followed by reaction of the intermediate imidazolide with (XIIA) at from about 35 to about 80°C. In another example, intermediate (IXA) could be coupled to the pyrazole (XIIA) in the presence of 1-hydroxybenzotriazole, triethylamine and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride.

It will be appreciated that salts of compounds (I) and (IA) of Schemes 1 and 4 can be formed in accordance with the invention by converting the relevant compound to a salt thereof (either *in situ* or as a separate step). For example base addition salts of the compounds of formulae (VI) and (XI) can be formed and can be utilised in accordance with the process of the present invention. Also the acid addition salts of the compounds of formulae (I) and (IA) can be formed in accordance with the invention.

By way of illustration, acid addition salts of compounds of formula (I) (more particularly (IA)) can be formed by reacting a compound of formula (I) with an equimolar or excess amount of acid. The salt may then be precipitated out of solution and isolated by filtration or the solvent can be stripped off by conventional means.

The pharmaceutically or veterinarily acceptable salts of the compounds of formulae (I) and (IA) which contain a basic centre are, for example, non-toxic acid addition

salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulphuric and phosphoric acid, with carboxylic acids or with organo-sulphonic acids. Examples include the HCl, HBr, HI, sulphate or bisulphate, nitrate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, saccarate, fumarate, maleate, lactate, citrate, tartrate, gluconate, camsylate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate and pamoate salts. Compounds (I) and (IA) can also provide pharmaceutically or veterinarily acceptable metal salts, in particular non-toxic alkali and alkaline earth metal salts, with bases. Examples include the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts. For a review on suitable pharmaceutical salts see Berge et al, J. Pharm, Sci., 66, 1-19, 1977.

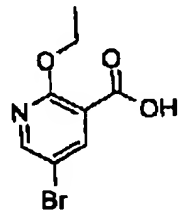
The pharmaceutically acceptable solvates of compounds (I) and (IA) include the hydrates thereof.

Suitable protecting groups for use in accordance with the invention can be found in "Protecting Groups" edited by P.J. Kocienski, Thieme, New York, 1994 - see particularly chapter 4, page 118-154 for carboxy protecting groups; and "Protective Groups in Organic Synthesis" 2nd edition, T.W. Greeene & P.G.M. Wutz, Wiley - Interscience (1991)- see particularly chapter 5 for carboxy protecting groups.

The process according to the present invention will now be described by way of example only with reference to the following examples.

Example 1. Preparation of Compound 1A – Route A

Preparation 1(a) Starting Material - 5-Bromo-2-ethoxynicotinic acid (preparation of VIA from VA)



A solution of potassium *t*-butoxide (183.6 g, 1.60 mol) in absolute ethanol (1200 mL) was added slowly to a solution of 2-chloronicotinic acid (120 g, 0.76 mol) in ethanol (400 mL), and the reaction heated in a sealed vessel at 170°C for 20 h. On cooling, the reaction mixture was concentrated under reduced pressure, the residue dissolved in water (800 mL) and acidified to pH 3 with aqueous hydrochloric acid. The aqueous solution was extracted with dichloromethane (4 x 800 mL), the organic phases combined, dried (Na_2SO_4) and concentrated under reduced pressure to afford the 2-ethoxy nicotinic acid (109.6 g, 41%) as a white solid [^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (t, 3H), 4.69 (q, 2H), 7.13 (m, 1H), 8.37 (d, 1H), 8.48 (d, 1H)]. 2-Ethoxynicotinic acid (83.6 g, 0.5 mol) was added portionwise to a mixture of trifluoroacetic acid/trifluoroacetic anhydride (TFA/TFAA) (350 mL of each) at room temperature with constant stirring. N-Bromo-succinamide (NBS) (89.0 g, 0.5 mol) was then added portionwise over 20 minutes before the reaction mixture was heated to reflux for 5 hours. The reaction was cooled to room temperature and allowed to stir overnight. The reaction was then poured into a 1:1 mixture of cooled brine / water (2 L). The resultant white solid was filtered, washed with water and dissolved in EtOAc (300 mL). The solution was dried over $MgSO_4$ and filtered. The filtrate was treated with hexane (1.2 L) and the resultant pale yellow precipitate was filtered and washed with 40-60 petroleum ether. The title compound was dried at 50°C under vacuum: m.p. = 122-124°C; 1H NMR (300 MHz, $CDCl_3$): δ = 1.53 (t, 3H), 2.64 (s, 3H), 4.67 (q, 2H), 8.42 (d, 1H), 8.57 (d, 1H).

Preparation 1(b) - 5-Acetyl-2-ethoxynicotinic acid (preparation of VIIIA from VIIA)

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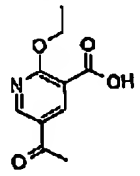
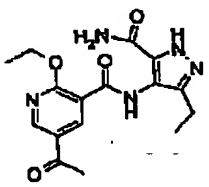


Triethylamine (354 mL, 2.54 M), was added to a slurry of 5-bromo-2-ethoxynicotinic acid (250g, 1.02 M) in acetonitrile (1 L). To this reaction mixture was added palladium (II) acetate (4.56 g, 20.3 mmol), butyl vinyl ether (305 g, 3.05 M) and tri-o-tolyl phosphine (12.4 g, 40.6 mmol), each addition being washed in with acetonitrile. Further acetonitrile (1 L) was then added and the reaction mixture heated to reflux under nitrogen for 22 hours. The reaction mixture was left at room temperature for 16 hours, and then the precipitate removed by filtration. The filtrate was concentrated *in vacuo* to give a brown gum, which was then stirred for 1 hour in water (1L) and concentrated HCl (1L). The reaction mixture was diluted with water (6.25 L), and extracted with dichloromethane (6 x 500 mL). The combined organic layers were extracted with 5% sodium bicarbonate solution (1.2 L, 2 x 400 mL). The basic aqueous extracts were washed with dichloromethane (250 mL), and then acidified to pH 3. After stirring for 30 minutes the precipitated product was removed by filtration, washed with water (250 mL) and dried at 50°C *in vacuo* to yield the target compound as a white solid (134 g, 64.1 mmol, 63%): 1H NMR (400 MHz, $CDCl_3$): δ = 1.56 (t, 3H, J = 7.1 Hz), 2.64 (s, 3H), 4.78 (q, 2H, J = 6.7 Hz), 8.96 (d, 1H, J = 2.6 Hz), 8.98 (d, 1H, J = 2.6 Hz); LRMS (*m/z*) (ES^-) 208 (MH^-)

Preparation 1(c) - 5-Acetyl-*N*-[3-(aminocarbonyl)-5-ethyl-1*H*-pyrazol-4-yl]-2-ethoxynicotinamide

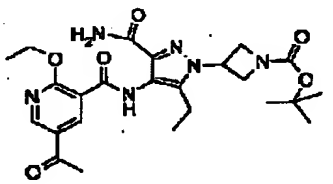


A solution of the title compound from Preparation 1(b) (5.70 g, 27.3 mmol) and *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluor-phosphate (10.9g,

28.6 mmol) in dichloromethane (100 mL) was added to a solution of 4-amino-3-ethyl-1*H*-pyrazole-5-carboxamide[i] (4.20 g, 27.3 mmol) and diisopropylethylamine (23.7 mL, 136.2 mmol) in dichloromethane (115 mL) under nitrogen. After 1h the mixture was diluted with brine (100 mL) and washed with a saturated aqueous sodium bicarbonate solution (100 mL) and 2N HCl (100 mL). Each aqueous layer was extracted with dichloromethane (100 mL), and the combined organics washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. An analytical sample of the title compound was obtained by trituration with ethyl acetate, followed by recrystallisation from ethanol, while the remainder was purified by column chromatography on silica gel (eluting with 95:5 CH_2Cl_2:MeOH) to yield the title compound as a white solid (total weight = 7.8 g, 22.5 mmol, 83%): mp 217-219°C; 1H NMR (400MHz, DMSO-d_6): δ = 1.10 (t, 3H, *J* = 7.6 Hz), 1.42 (t, 3H, *J* = 7.1 Hz), 2.56 (s, 3H), 2.73 (q, 2H, *J* = 7.6 Hz), 4.62 (q, 2H, *J* = 6.9 Hz), 7.26 (br s, 1H), 7.48 (br s, 1H), 8.71 (d, 1H, *J* = 1.8 Hz), 8.91 (d, 1H, *J* = 2.4 Hz), 10.52 (br s, 1H), 12.93 (br s, 1H); LRMS (*m/z*) (TSP$^+$) 346.2 (MH^+).

Preparation 1(d)

tert-Butyl 3-[4-{[(5-acetyl-2-ethoxy-3-pyridinyl)carbonyl]amino}-3-(aminocarbonyl)-5-ethyl-1*H*-pyrazol-1-yl]-1-azetidinecarboxylate

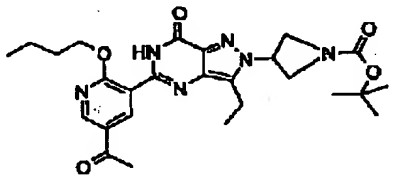


Cesium carbonate (46.4 g, 142 mmol) was added to a stirring solution of the title compound of Preparation 1(c) (32.8 g, 95.0 mmol) and *tert*-butyl-3-iodo-1-azetidinecarboxylate[ii] (40.4 g, 143 mmol) in N,N-dimethylformamide (400 mL), and the reaction mixture was heated at 50°C for 16 hours. The solvent was then removed *in vacuo*, and the residue triturated from ethyl acetate (100 mL). The resulting solid was filtered off, washed with ethyl acetate and partitioned between dichloromethane (500 mL) and water (300 mL) in the presence of concentrated hydrochloric acid (5 mL). The organic layer was separated, and the aqueous layer was extracted further with dichloromethane (2 x 100 mL). The combined organic

layers were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting crude product was triturated from acetonitrile, filtered and washed with acetonitrile and ether to yield the title compound as a white solid (30.3 g, 60.0 mmol, 63%): mp 220-223°C; 1H NMR (400MHz, $CDCl_3$): δ = 1.15 (t, 3H, *J* = 7.6 Hz), 1.44 (s, 9H), 1.54 (t, 3H, *J* = 7.1 Hz), 2.57 (s, 3H), 2.83 (q, 2H, *J* = 7.3), 4.32 (t, 2H, *J* = 8.1 Hz), 4.37-4.46 (m, 2H), 4.74 (q, 2H, *J* = 7.1 Hz), 5.02-5.10 (m, 1H), 5.33 (br s, 1H), 6.72 (br s, 1H), 8.85 (d, 1H, *J* = 2.5 Hz), 8.98 (d, 1H, *J* = 2.4 Hz), 10.49 (br s, 1H); LRMS (*m/z*) (ES^+) 523.0 (MNa^+), (ES^-) 499.0 (MH^-).

Preparation 1(e)

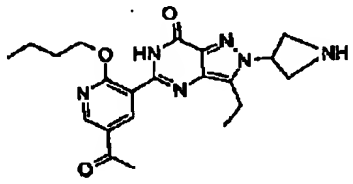
tert-Butyl 3-[5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-7-oxo-6,7-dihydro-2*H*-pyrazolo[4,3-*d*]pyrimidin-2-yl]-1-azetidinecarboxylate



The title compound of Preparation 1(d) (30.3 g, 60.0 mmol) and cesium carbonate (40.0 g, 123 mmol) were dissolved in *n*-butanol (500 mL) in the presence of 3Å molecular sieves (5.00 g), and heated under reflux for 6h. The first 90 mL of solvent were removed *via* distillation. The reaction mixture was then left at room temperature for 16h, before being concentrated *in vacuo*. The residue was partitioned between ethyl acetate (400 mL) and water (400 mL), and solid carbon dioxide added until pH8. The organic layer was then separated, and the aqueous extracted further with ethyl acetate (400 mL). The combined organic layers were then dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (eluting with CH_2Cl_2:MeOH:0.88NH_3 98:2:0.2 to 96:4:0.4), followed by crystallisation from diisopropylether. This yielded the title compound, containing a 10% impurity, as white crystals (13.5 g, 26.4 mmol, 46%): mp 176-178°C; 1H NMR (400MHz, $CDCl_3$): δ = 0.98 (t, 3H, *J* = 7.6 Hz), 1.33 (t, 3H, *J* = 7.6 Hz), 1.44 (s, 9H), 1.48–1.54 (m, 2H), 1.85–1.95 (m, 2H), 2.62 (s, 3H), 3.00 (q, 2H, *J* = 7.6 Hz), 4.34 (t, 2H, *J* = 6.8 Hz), 5.19-5.27 (m, 1H), 8.82 (d, 1H, *J* = 2.4 Hz), 9.21 (d, 1H, *J* = 2.4 Hz), 10.64 (br s, 1H); LRMS (*m/z*) (ES^+) 433 (MNa^+), (ES^-) 509 (MH^-).

Preparation 1(f)

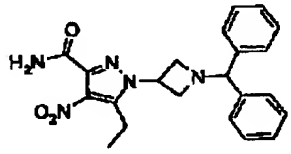
5-(5-Acetyl-2-butoxy-3-pyridinyl)-2-(3-azetidinyl)-3-ethyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one



Trifluoroacetic acid (25 mL, 31%vol) was added to a solution of the title compound of Preparation 1(e) (13.4 g, 262 mmol) in dichloromethane (80 mL) at 0°C, and the mixture was then stirred at room temperature for 1hour. The reaction mixture was poured into toluene (100 mL) and concentrated *in vacuo* to yield an oil. The oil was azeotroped again with toluene (50 mL), and the residue taken up in *iso*-propylacetate. The resulting precipitate was removed by filtration and dried *in vacuo* to yield the trifluoacetate salt of the title compound as a white solid (11.2 g, 17.5 mmol, 67%): 1H NMR (400MHz, DMSO-d_6): δ = 0.87 (dt, 3H, *J* = 1.5, 7.3 Hz), 1.19 (t, 3H, *J* = 7.3 Hz), 1.35-1.44 (m, 2H), 1.63-1.72 (m, 2H), 2.58 (s, 3H), 2.92 (q, 2H, *J* = 7.8 Hz), 3.78 (t, 2H, *J* = 7.6 Hz), 4.05-4.11 (m, 2H), 4.34-4.43 (m, 2H), 5.45-5.53 (m, 1H), 8.39 (d, 1H, *J* = 1.5 Hz), 8.90 (d, 1H, *J* = 1.5 Hz); LRMS (*m/z*) (ES^+) 411.0 (MH^+), (ES^-) 409.0 (MH^-)

Preparation 2(a)

1-(1-Benzhydryl-3-azetidinyl)-5-ethyl-4-nitro-1*H*-pyrazole-3-carboxamide



The title compound was prepared by either of the following methods;

a) 5-Ethyl-4-nitro-1*H*-pyrazole-3-carboxamide (WO 98/49166) (25.0g, 136 mmol), sodium carbonate (57.6 g, 543 mmol), sodium iodide (40.7 g, 272 mmol) and 1-

benzhydryl-3-azetidinyl methanesulfonate (86.2 g, 272 mmol) were suspended in tetrahydrofuran (338 mL) and water (38 mL) and heated under reflux for 5 days. The reaction mixture was then concentrated *in vacuo* and taken up in ethyl acetate (500 mL) and water (300 mL). The resulting precipitate was filtered, washed with ethyl acetate and water to yield the title compound as a white solid (17g, 41.9 mmol, 31%): mp 257-260°C; 1H NMR (400MHz, DMSO-d_6): δ = 1.09 (t, 3H, J = 7.6 Hz), 2.95 (q, 2H, J = 7.3 Hz), 3.43 (t, 2H, J = 7.6 Hz), 3.61 (t, 2H, J = 7.6 Hz), 4.59 (s, 1H), 5.23 (quintet, 1H, J = 7.3 Hz), 7.15-7.20 (m, 2H), 7.24-7.31 (m, 4H), 7.43-7.48 (m, 4H), 7.70 (br s, 1H), 7.95 (br s, 1H); LRMS (*m/z*) (TSP$^+$) 406.2 (MH^+).

b) 5-Ethyl-4-nitro-1*H*-pyrazole-3-carboxamide[1] (800.0 g, 4.34 mol), sodium carbonate (1845 g, 17.4 mol), sodium iodide (965 g, 6.44 mol) and 1-benzhydryl-3-azetidinyl methanesulfonate (1837 g, 5.8 mol) were suspended in tetrahydrofuran (10.8 L) and water (1.2 L) and heated under reflux for 5 days with constant stirring. The reaction mixture was then distilled at atmospheric pressure so that 7.5 L of solvent was distilled. The reaction was cooled to 40°C and water (8 L) was added to the reaction mixture. The reaction mixture was again heated while solvent was distilled at atmospheric pressure. In this distillation the internal temperature rose to 98°C and 900 mL of solvent was collected. The reaction was cooled to 80°C and MIBK (2.4 L) was added the reaction mixture was then heated to reflux for 1h and allowed to cool to room temperature overnight. The resulting precipitate was cooled to 12°C and granulated for 2 hours before filtering. The filter cake was washed with water (2 L) and MIBK (2 L). The solid product was oven dried at 50°C under vacuum. The resultant yellow solid was reslurried in water (9 L) at room temperature for 3 hours before being filtered under vacuum. The filter cake was washed with MIBK (1 L) with gentle agitation using a spatula. The pale cream solid was oven dried at 50°C under vacuum to afford the title compound (758 g, 43%): Data as reported above.

Preparation 2(b)

1-(3-Azetidinyl)-5-ethyl-4-nitro-1*H*-pyrazole-3-carboxamide

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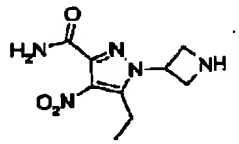
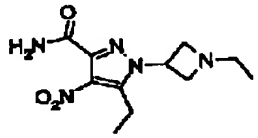


To a suspension of the title compound of Preparation 2(a) (35.3 g, 87.1 mmol) in dichloromethane (700 mL) at 0°C under nitrogen was added 1-chloroethyl chloroformate (10.4 mL, 95.8 mmol) dropwise. The reaction mixture was stirred at 0°C for 30 minutes, and at room temperature for 18 hours. The reaction mixture was then concentrated *in vacuo*, and the oily residue dissolved in methanol (700 mL) and refluxed for 1hour. The solvent was then removed *in vacuo*, and the crude product triturated from ethyl acetate (200 mL) and acetone (200 mL) to yield the dihydrochloride salt of the title compound as a beige solid (21.3 g, 77.3 mmol, 89%): mp 164-167°C; 1H NMR (400MHz, DMSO-d_6): δ = 1.09 (t, 3H, J = 7.6 Hz), 2.92 (q, 2H, J = 7.3 Hz), 4.26-4.40 (m, 4H), 4.44-4.51 (m, 1H), 7.75 (br s, 1H), 8.01 (br s, 1H), 9.39 (br s, 2H); LRMS (*m/z*) (TSP$^+$) 240.3 (MH^+).

Preparation 2(c)

5-Ethyl-1-(1-ethyl-3-azetidinyl)-4-nitro-1*H*-pyrazole-3-carboxamide

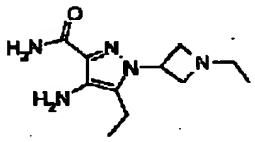


To a stirring solution of the title compound of Preparation 2(b) (31.1 g, 113 mmol) and triethylamine (14.1 mL, 102 mmol) in dichloromethane (400 mL) and methanol (400 mL) at 0°C, was added sodium triacetoxyborohydride (60 g, 282 mmol) in one portion. Acetaldehyde (19 mL, 339 mmol) was then added dropwise over 2 minutes. The reaction mixture was then allowed to warm up to room temperature over 30 minutes. The solvent was then removed *in vacuo*, and the residue partitioned between dichloromethane (500 mL) and water (300 mL). The organic layer was separated, and the aqueous layer basified with solid sodium bicarbonate and extracted with dichloromethane (500 mL) and dichloromethane:methanol (95:5, 500 mL; 90:10, 500 mL). The combined organic layers were dried ($MgSO_4$), and

concentrated *in vacuo*. The residue was triturated from hot ethyl acetate, and a white solid separated by filtration. The filtrate was concentrated *in vacuo*, and purified by flash column chromatography (eluting with CH_2Cl_2:MeOH:0.88NH_3 95:5:0.5) to give a white solid which was combined with the previous batch to yield the title compound (23.3g, 86.8 mmol, 77%): mp 177-179°C; 1H NMR (400MHz, $CDCl_3$): δ = 1.01 (t, 3H, *J* = 7.3 Hz), 1.25 (t, 3H, *J* = 7.6 Hz), 2.62 (q, 2H, *J* = 7.3 Hz), 2.95 (q, 2H, *J* = 7.8 Hz), 3.55 (dt, 2H, *J* = 2.0, 6.4 Hz), 3.83 (dt, 2H, *J* = 2.0, 6.8 Hz), 4.96 (quintet, 1H, *J* = 7.3 Hz), 6.13 (br s, 1H), 6.92 (br s, 1H); LRMS (*m/z*) (TSP⁺) 268.3 (MH^+).

Preparation 2(d)

4-Amino-5-ethyl-1-(1-ethyl-3-azetidinyl)-1*H*-pyrazole-3-carboxamide



A mixture of the title compound from Preparation 2(c) (22.0 g, 82.3 mmol) and 10% palladium on charcoal (2.0 g) in ethanol (500 mL) was hydrogenated at 60 p.s.i. and room temperature for 4hours. The reaction mixture was then filtered through Arbocel ® under nitrogen, and the filtrate was concentrated *in vacuo* to yield the title compound as a cream solid (19.6 g, 82.6 mmol, 100%): mp 155-157°C; 1H NMR (400MHz, $CDCl_3$): δ = 1.01 (t, 3H, *J* = 7.2 Hz), 1.13 (t, 3H, *J* = 7.6 Hz), 2.54 (q, 2H, *J* = 7.8 Hz), 2.59 (q, 2H, *J* = 7.3 Hz), 3.46 (t, 2H, *J* = 7.8 Hz), 3.77 (t, 2H, *J* = 7.6 Hz), 3.93 (br s, 2H), 4.83 (quintet, 1H, *J* = 7.3 Hz), 5.25 (br s, 1H), 6.64 (br s, 1H); LRMS (*m/z*) (TSP⁺) 238.2 (MH^+).

Preparation 2(e)

5-Acetyl-*N*-[3-(aminocarbonyl)-5-ethyl-1-(1-ethyl-3-azetidinyl)-1*H*-pyrazol-4-yl]-2-ethoxynicotinamide

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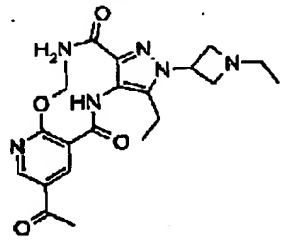
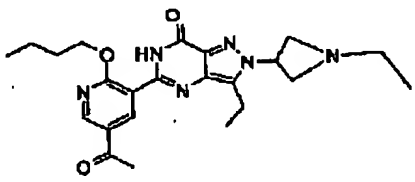


1,1-Carbonyldiimidazole (13.9 g, 85.8 mmol) was added to a suspension of the title compound from Preparation 1(b) (17.1 g, 81.8 mmol) in ethyl acetate (140 mL) under nitrogen, and the reaction mixture was stirred at 45°C for 45 minutes and heated under reflux for 90 minutes. The reaction mixture was then cooled to room temperature and a slurry of the title compound from Preparation 9 (19.4 g, 81.8 mmol) in ethyl acetate (70 mL) was added. The reaction mixture was then heated under reflux for 16hours, after which a precipitate had formed. The suspension was cooled to room temperature and the solid removed by filtration. The solid was washed with water:ethanol 90:10 and then dried *in vacuo* to yield the title compound as a white solid (24.0 g, 56.0 mmol, 69%): mp 230-233°C; 1H NMR (400MHz, $CDCl_3$): δ = 1.03 (t, 3H, *J* = 7.3 Hz), 1.20 (t, 3H, *J* = 7.8 Hz), 1.57 (t, 3H, *J* = 7.3 Hz), 2.60 (s, 3H), 2.62 (q, 2H, *J* = 6.8 Hz), 2.86 (q, 2H, *J* = 7.3 Hz), 3.53 (t, 2H, *J* = 7.8 Hz), 3.83 (t, 2H, *J* = 7.3 Hz), 4.77 (q, 2H, *J* = 6.8 Hz), 4.99 (quintet, 1H, *J* = 7.3 Hz), 5.30 (br s, 1H), 6.74 (br s, 1H), 8.89 (d, 1H, *J* = 2.4 Hz), 9.02 (d, 1H, *J* = 2.4 Hz), 10.48 (br s, 1H); LRMS (*m/z*) (TSP$^+$) 429.2 (MH^+).

Example 1A

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one



Route A: Potassium carbonate (4.80 g, 34.7 mmol) and ethyl iodide (1.4 mL, 17.5 mmol) were added to a cloudy solution of the title compound from Preparation 1(f) (11.1 g, 17.4 mmol) in acetonitrile (600 mL), and then the reaction mixture was heated to 45-50°C for 2.5h. The solvent was then removed *in vacuo*, and the residue dissolved in dichloromethane:methanol:ammonia 95:5:0.5 (50 mL). The resulting solution was filtered, and then purified by column chromatography on silica gel (eluting with CH_2Cl_2:MeOH:0.88NH_3 95:5:0.5 to 92:8:1). The product was crystallised from diisopropylether to yield the title compound as white crystals (4.90 g, 11.2 mmol, 64%).

Route B: Cesium carbonate (38.6 g, 119 mmol) was added to a solution of the title compound from Preparation 2(e) (25.4 g, 59.3 mmol) in *n*-butanol (400 mL) in the presence of powdered 3A molecular sieves (10 g). The reaction mixture was then heated to reflux, and 20 mL of solvent removed *via* distillation into a splash trap. Refluxing was then continued for 4h, after which the reaction mixture was cooled and filtered. The filtrate was concentrated *in vacuo*, and then purified by column chromatography on silica gel (eluting with CH_2Cl_2:MeOH:0.88NH_3 95:5:0.5) to yield a green oil. The crude product was then purified by crystallisation from ethyl acetate, to yield the title compound as a white solid (9.00 g, 20.5 mmol, 35%): mp 143.0-144.0°C; 1H NMR (400MHz, DMSO-d_6): δ = 1.01 (t, 3H, J = 7.3 Hz), 1.03 (t, 3H, J = 7.3 Hz), 1.37 (t, 3H, J = 7.8 Hz), 1.49-1.59 (m, 2H), 1.89-1.97 (m, 2H), 2.65 (s, 3H), 2.66 (q, 2H, J = 7.3 Hz), 3.03 (q, 2H, J = 7.3 Hz), 3.72 (t, 2H, J = 7.8 Hz), 3.90 (t, 2H, J = 7.8 Hz), 4.68 (t, 2H, J = 6.8 Hz), 5.12-5.19 (m, 1H), 8.85 (d, 1H, J = 2.4 Hz), 9.23 (d, 1H, J = 2.4 Hz), 10.62 (br s, 1H); LRMS (*m/z*) (TSP$^+$) 439.2 (MH^+); Anal. Found C, 63.00; H, 6.92; N, 19.14; Calcd for $C_{23}H_{30}N_6O_3$ C, 63.00; H, 6.90; N, 19.16.

2. Preparation of Compound 1A – Route B

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

To a stirred suspension of 5-Acetyl-*N*-[3-(aminocarbonyl)-5-ethyl-1-(1-ethyl-3-azetidinyl)-1*H*-pyrazol-4-yl]-2-ethoxynicotinamide (0.41 g, 0.96 mMol) in *n*-butanol (4 mL) under nitrogen atmosphere at room temperature was added *n*-butyl acetate (1.92 mMol, 0.25 mL) followed by potassium *tert*-butoxide (14.4 mMol, 162 mg) as a single solid portion. The reaction was left to stir at room temperature for 5 minutes before being heated to reflux overnight. The reaction was not complete so further *n*-butyl acetate (1.92 mMol, 0.25 mL) and potassium *tert*-butoxide (1.92 mMol, 215 mg) were added and the reaction was heated to reflux for a further 2h. The reaction was allowed to cool to room temperature and then reduced to low volume (ca 1mL) at reduced pressure. The crude concentrate was then diluted with DCM (50 mL) and washed with water (50 mL). The bi-phasic mixture was then passed through a pad of celite and the cake was washed with further DCM (50 mL). The two phases were then treated with brine (20 mL) and separated. The aqueous phase was then extracted with DCM (3 x 40 mL). The combined organics were then evaporated at reduced pressure to afford a dark brown oil that appeared to contain residual *n*-butanol. The crude residue was triturated with hexane (10 mL) and the resultant tan solid isolated by decanting the liquors to afford the title compound, 0.50 g, yield by HPLC = 50%. M/Z = 439 $(M+H)^+$.

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one

To a stirred suspension of 5-Acetyl-*N*-[3-(aminocarbonyl)-5-ethyl-1-(1-ethyl-3-azetidinyl)-1*H*-pyrazol-4-yl]-2-ethoxynicotinamide (1.07 g, 2.5 mMol) in *n*-butanol (10 mL) under nitrogen atmosphere at room temperature was added *n*-butyl acetate (7.5 mMol, 0.87 mL) followed by potassium carbonate (7.5 mMol, 1.04mg) as a single solid portion. The reaction was left to stir at room temperature for 5 minutes before being heated to reflux for 24 hours. The reaction was allowed to cool to room temperature and then reduced to low volume (ca 2 to 3 mL) at reduced pressure. The crude concentrate was then diluted with water (20 mL), this aqueous mixture was then treated with dilute HCl until pH 7 was attained at which point the remaining solvent was azeotroped out under reduced pressure. The resulting precipitate was

cooled and filtered and the solid product dried to afford the title compound, 1.09 g, yield by HPLC = 81%. M/Z = 439 $(M+H)^+$.

Thus the process according to the present invention (i.e. the hydroxide trapping agent) is more efficient for the preparation of compounds 1A and provides improved yields. In particular the cyclisation of compound IIIA to IA as exemplified herein provides the desired material in 81% yield whereas the corresponding reaction sequence in WO 01/27112 provides a yield of 35%.

Additionally, in accordance with the invention, the intermediate compounds (IX) (more particularly (IXA)) can be prepared from commercially available starting materials (2-chloro or 2-hydroxy nicotinic acid) in better yield than the corresponding reaction sequence in WO 01/27112.

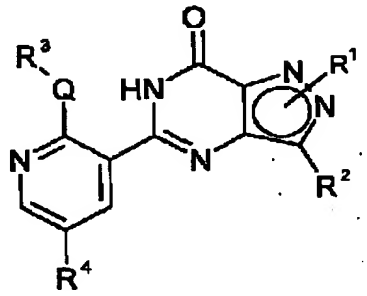
More particularly compounds of general formula (IA) can be prepared in an overall yield of 35% (from the corresponding intermediate compounds (VI) and (XIA)) according to the process of the present invention, as opposed to a yield of 9% via the process detailed in WO 01/27112. Furthermore, the reaction scheme of the present invention is safer and cheaper to operate, and in the case of the process for the preparation of intermediates (IX)/(IXA) also involves less steps (and processing time).

In a preferred aspect compounds of formula (I) and (IA) are prepared from 2-hydroxy nicotinic acid or 2-chloro nicotinic acid in accordance with Schemes 1 and 2.

Thus, in a preferred aspect of the invention there is provided a process for the preparation of a compound of formula (I) and (IA) according to the Scheme 4 as hereinbefore detailed.

Claims

1. A process for the preparation of a compound of general formula (I):



I

or a pharmaceutically or veterinarily acceptable salt , pro-drug, polymorph and/or solvate thereof, wherein

Q represents O or NR^5

R^1 represents H, lower alkyl, Het, alkylHet, aryl or alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

R^2 represents H, halo, cyano, nitro, OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$, $SO_2NR^{14}R^{15}$, lower alkyl, Het, alkylHet, aryl or alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

R^3 represents H, lower alkyl, alkylHet or alkylaryl (which latter three groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

R^4 represents H, halo, cyano, nitro, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$, $NR^{16}Y(O)R^{17}$, $N[Y(O)R^{17}]_2$, SOR^{18},

SO_2R^{19}, C(O)AZ, lower alkyl, lower alkenyl, lower alkynyl, Het, alkylHet, aryl, alkylaryl (which latter seven groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

Y represents C or S(O)

A represents lower alkylene

Z represents OR^6, halo, Het or aryl (which latter two groups are both optionally substituted with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

R^{10} and R^{11} independently represent H or lower alkyl (which latter group is optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6, $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10a}R^{11a}$, $NR^{12}R^{13}$, $SO_2NR^{14}R^{15}$ and $NR^{20}S(O)_2R^{21}$ or Het or aryl optionally substituted with one or more of said latter thirteen groups) or one of R^{10} and R^{11} may be lower alkoxy, amino or Het, which latter two groups are both optionally substituted with lower alkyl

R^{10a} and R^{11a} independently represent R^{10} and R^{11} as defined above, except that they do not represent groups that include lower alkyl, Het or aryl, when these three groups are substituted and/or terminated (as appropriate) by one or more substituents that include one or more $C(O)NR^{10a}R^{11a}$ and/or $NR^{12}R^{13}$ groups

R^{12} and R^{13} independently represent H or lower alkyl (which latter group is optionally substituted and/or terminated with one or more substituents selected from OR^8, $C(O)OR^9$, $C(O)NR^{22}R^{23}$ and $NR^{24}R^{25}$), one of R^{12} or R^{13} may be C(O)-lower alkyl or C(O)Het (in which Het is optionally substituted with lower alkyl), or R^{12} and R^{13} together represent C_{3-7} alkylene (which alkylene group is optionally unsaturated, optionally substituted by one or more lower alkyl groups and/or optionally interrupted by O or NR^{26})

R^{14} and R^{15} independently represent H or lower alkyl or R^{14} and R^{15}, together with the nitrogen atom to which they are bound, form a heterocyclic ring

R^{16} and R^{17} independently represent H or lower alkyl (which latter group is optionally substituted and/or terminated with one or more substituents selected from OR^6, $C(O)OR^9$, $C(O)NR^{22}R^{23}$ and $NR^{24}R^{25}$) or one of R^{16} and R^{17} may be Het or aryl, which latter two groups are both optionally substituted with lower alkyl

R^5, R^6, R^7, R^8, R^9, R^{18}, R^{19}, R^{20}, R^{22}, R^{23}, R^{24} and R^{25} independently represent H or lower alkyl

R^{18} and R^{19} independently represent lower alkyl

R^{21} represents lower alkyl or aryl

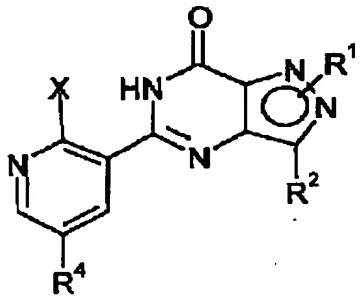
R^{26} represents H, lower alkyl, aryl, $C(O)R^{27}$ or $S(O)_2R^{28}$

R^{27} represents H, lower alkyl or aryl

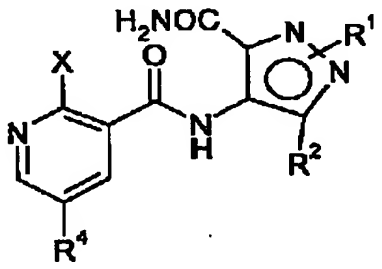
R^{28} represents lower alkyl or aryl

Het represents an optionally substituted four- to twelve-membered heterocyclic group, which group contains one or more heteroatoms selected from nitrogen, oxygen, sulphur and mixtures thereof

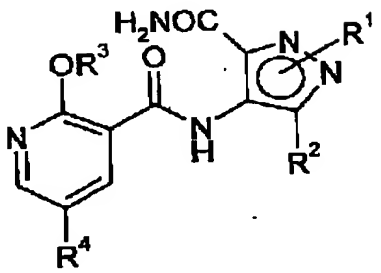
said process comprising reacting a compound of formula (II), (III), (IV) or (V) in the presence of $^-OR^3$ and a hydroxide trapping agent or, alternatively, in the case of compounds of formulae (IV) or (V) reacting in the presence of an auxiliary base and a hydroxide trapping agent (i.e. $^-OR^3$ is substituted by the auxiliary base)



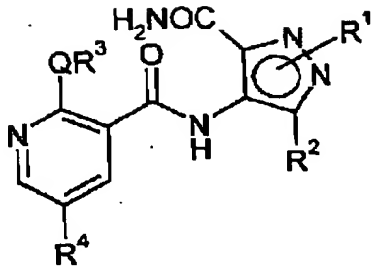
(II)



(III)



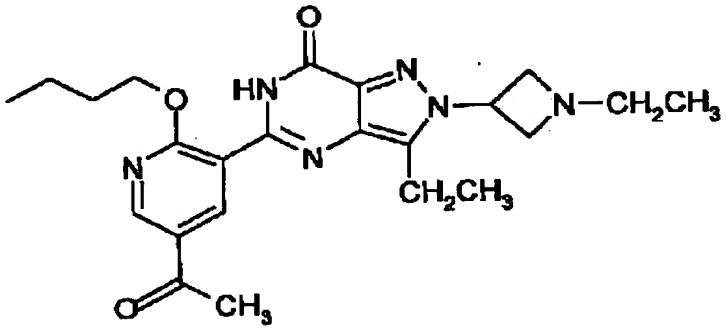
(IV)



(V)

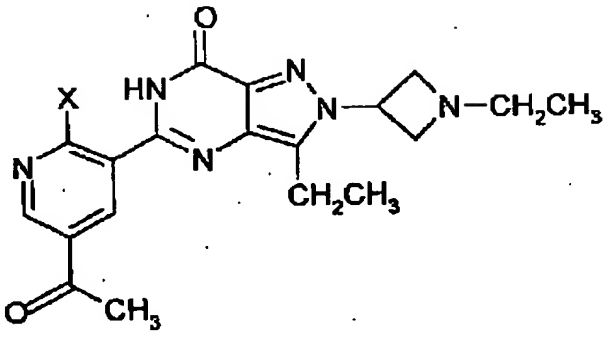
wherein X is a leaving group and Q and R^1 to R^4 are as defined above.

2. A process for the preparation of a compound of formula (IA):

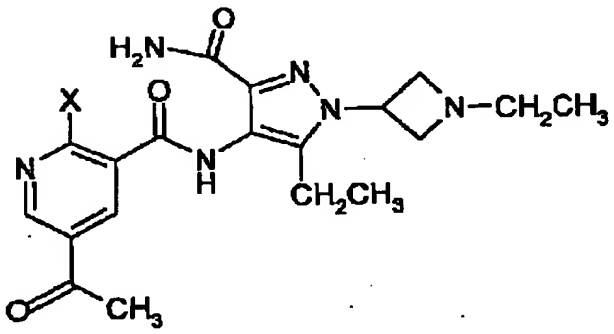


(IA)

said process comprising reacting a compound of formula (IIA), (IIIA) or (IVA) respectively



(IIA)



(IIIA)

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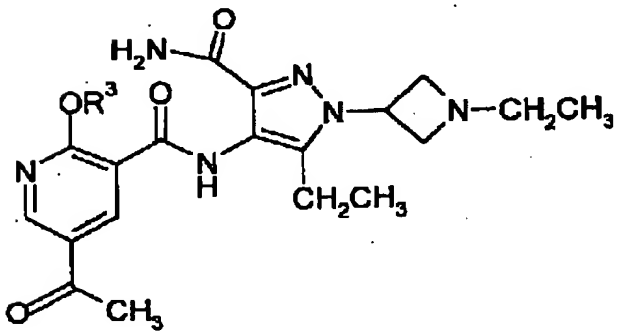

(IVA)

in the presence of $^{-}OR^{3}$ and a hydroxide trapping agent, or alternatively in the case of compounds of formula (IVA) reacting in the presence of a hydroxide trapping agent and an auxiliary base, wherein OR^{3} in the case of formation of compound (IA) and (IVA) is $CH_3(CH_2)_3O$- and wherein X in formulae (IIA) and (IIIA) is a leaving group.

Abstract

A process is provided for the preparation of compounds of formula (I) herein comprising reacting a compound of formula (II), (III), (IV) or (V) in the presence of $-OR^3$ and a hydroxide trapping agent or in the case of compounds of formula (IV) reacting in the presence of an auxiliary base and a hydroxide trapping agent (i.e. $-OR^3$ is substituted by the auxiliary base), wherein X is a leaving group and R^1 to R^4 are as defined.